The Chemistry of Hypervalent Iodine

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Key References:
P. Stang, V. V. Zhdankin, Chem. Rev. 96, 1123-1178 (1996)

Background and Introduction

Iodine is most commonly in monovalent compounds with an oxidation state of -1, however, because it is the largest, most polarizable, and most electropositive of the group 17 elements, it also forms stable polycoordinate, multivalent compounds.

First polyvalent organic iodine complex, (dichloroiodo)benzene or PhICl₂, was prepared was by German chemist C. Willgerodt in 1866. Although it's oxidizing properties were known since 1893, a renaissance in the field of polyvalent iodine has occured only in the past 20 years.

Factors leading to resurgence of interest:
(1) Chemical properties and reactivity is similair to the heavy metal reagents such as Hg(III), Ti(III), Pb(IV) but without the toxicity & environmental issues.
(2) Mild reaction conditions and easy handling of hypervalent iodine compounds
(3) Commercial availability of key precursors such as PhI(OAc)₂

Topics to be covered in this talk:
Nomenclature, Structures, and Properties
Reactivity Pattern and Mechanisms of Organoc–I–Iodanes: RIL₂ and R₂IL
Survey of Reactive Transformations Using Hypervalent Iodine Reagents
Selected Applications in Total Synthesis

Topics that are NOT covered in this talk: Transition Metal Mediated Reactions and Polymer Supported Reagents
Nomenclature for Hypervalent Iodine

- The term hypervalent was established in 1969 for molecules with elements of groups 15-18 bearing more electrons than an octet in their valence shell.
- IUPAC rules designate \( \square \) as non-standard bonding; thus, \( \text{H}_2\text{I} \) is \( \square^2 \)-iodane and \( \text{H}_3\text{I} \) is \( \square^3 \)-iodane. Most common decet structure is aryl\( \square^2 \)-iodane \( \text{ArI}_2 \) (\( L \) = heteroatom) and for dodecet structure is aryl\( \square^3 \)-iodane \( \text{ArI}_3 \).
- Polyvalent iodine species differ in Martin-Arduengo designation \( [N-X-L] \) where \( N \) = # of valence electrons on central atom, \( X \) = central atom, \( L \) = # of ligands on central atom.

\[
\begin{align*}
\text{Iodinanes: trivalent iodine} & \quad \text{Periodinanes: pentavalent iodine} \\
\text{Cl}^- & \quad \text{Ar} \\
\text{Ph} & \quad \text{L}_{n}=\text{L} \\
\text{Ph} & \quad \text{L} \\
8-1-2 & \quad 12-1-5 \\
\text{tetrahedral} & \quad \text{square pyramid}
\end{align*}
\]

- Diphenyliodonium chloride vs. Chloro(diphenyl)-\( \square^3 \)-iodane?

Onium salts (such as ammonium, phosphonium,oxonium, etc.) refers to a tetrahedral geometry with an octet in the valence shell of a positively charged atom and are not hypervalent compounds. Also, X-ray structural data of iodine(III) compounds with a coordination of 2 (as in iodonium salts) have never been observed.

Classes of Hypervalent Iodine

- Traditional classification is based on the # of carbon ligands on central iodine.
  
  **For Iodinanes**
  
  - TC-bond: Iodosyl iodosyl compounds (RIO) and their derivatives (RIX₂, where \( X = \) non-carbon ligands and \( R = \) aryl or CF₃)
  - 2 C-bonds: Iodonium salts (RI⁺X⁻)
  - 3 C-bonds: Iodanes with 3 C-1 bonds are thermally unstable and not synthetically useful

  **For Periodinanes**
  
  - TC-bond: Iodyl/iodoxy compounds (RIO₂) and their derivatives (RIX₄ or RIX₂O)
  - 2 C-bonds: Iodyl salts (RI⁺O⁺X⁻)

- Compounds with more than one formal carbon bond to iodine:
  
  **Alkenyliodonium** (Ph⁺C=CHR X⁻) and **Alkynyliodonium** (Ph⁺C=CR X⁻) **Salts**
  
  **Iodonium Ylides** (Ph⁺=CXY, where \( X, Y = \) electron acceptors)

- Cyclic Iodinanes:
  
  \( \square^2 \)-Iodinanes: Benziodoxazole based on o-iodosobenzoic acid.

  \( \square^3 \)-Iodinanes: Benziodoxazole based on o-iodoxybenzoic acid. (ie. IBX and Dess-Martin Reagent)

- \( \square^4 \)-Oxo-bridged Iodanes (Ph⁺X(O)(X)Ph₊ where \( X = \) OTf, ClO₄⁻, BF₄⁻, PF₆⁻, SbF₆⁻)
Established Hypervalent Iodide Reagents

- Most Frequently Used Reagents

- IBX Related Reagents

- Newer Iodine(III) Reagents

Physical Aspects of $\text{I}^3$-iodanes

- Most hypervalent iodine reagents are solid (amorphous or crystalline) and are stable to atmospheric oxygen and moisture. Certain iodonium salts are less stable and should be generated in situ. A mild explosion will occur if heated in the absence of solvent for Phil(OMe)$_2$, PhilO, PhilO$_2$, (Phil)$_2$O 2BF$_4$, and o-iodobenzoic acid.

- In the solid state: Iodosybenzene and (tosyliminoiodo)benzene are polymeric structures terminated by water, HO(PhilO)$_2$.H. Monomeric species are generated in reactive solvents. Secondary I-O bonds are also observed and result in macrocyclic structures.

- In solution:
  Diaryl-$\text{I}^3$-iodanes (Ar$_2$I, where L = BF$_4$, Cl, Br, OAc) in polar solvents show extensive dissociation into solvated iodonium ions (Ar$_2$I$^+$ where S = H$_2$O, MeOH, and DMSO)

  Alkeny-$\text{I}^3$-iodanes exist in equilibrium as an iodonium ion and as a halogen-bridged dimeric and aggregate structures.
General Reactivity of Hypervalent Iodine

- Hypervalent iodine chemistry is based on the strongly electrophilic nature of the iodine making it susceptible to nucleophilic attack, in combination with the leaving group ability of phenyliodonio group -IPhX (~10^6 times greater than triflate!!!). The favorable reduction of the hypervalent iodide to normal valency by reductive elimination of iodobenzene is the key to its reactivity.

- Organo-[^3]-iodanes have reactivity based on the number of carbon and heteroatom ligands. They generally fit in two classes:
  1. RIL2: Majority of reactions fit under this category. Performs oxidation of various functional groups. The two heteroatoms occupying the apical sites of the pseudotrigonal bipyramid are essential. One is used in ligand exchange and the other in reductive elimination.

**Ligand Exchange**

![Ligand Exchange Diagram]

**Reductive Elimination of the Hypernucleofuge**

![Reductive Elimination Diagram]

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Reductive [\(\cdot\)]- and [\(\cdot\)]-Elimination of RIL2 Organo-[^3]-Iodanes

**Reductive [\(\cdot\)]Elimination:** Provides a method for the generation of carbenes.

![Reductive [\(\cdot\)] Elimination Diagram]

**Example:**

![Example Diagram]

**Reductive [\(\cdot\)]-Elimination**

On carbon atoms (M=C) produces C=C multiple bonds:

![Multiple Bond Formation Diagram]

Oxygen and nitrogen atoms (M-O and N) provides oxidation of benzylic/allylic alcohols and amines to the corresponding carbonyl and imine compounds. (i.e. Des-Martin [^3]-iodane oxidations)

![Des-Martin Oxidation Diagram]
More Reductive Eliminations of RIL₂ Organo-[^3]-iodanes

**Reductive Elimination with Fragmentation**

![Chemical diagram showing reductive elimination with fragmentation.]

**Reductive Elimination with Substitution**: Elimination of [^3]-iodanes with 2 carbon ligands with attack by a nucleophile on the carbon atom attached to the iodine(III) gives substitution products.

Example:

![Chemical diagram showing reductive elimination with substitution.]

**Reductive Elimination with Rearrangement**: Elimination with concomitant 1,2-alkyl or aryl shift gives rearranged products.

Example:

![Chemical diagram showing reductive elimination with rearrangement.]

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Reductive Elimination by Ligand Coupling of RIL₂ Organo-[^3]-iodanes

**Ligand Coupling**

![Chemical diagram showing ligand coupling.]

Example:

![Chemical diagram showing an example of ligand coupling.]

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Other Mechanisms of RIL₂ Organo-IP₃-iodanes

Homolytic Cleavage: Photochemical decomposition of a hypervalent I-O bond generates a reactive radical.

(Diacetyloxyido)arenes

Alkyloperoxy-I₃-iodanes

Other Mechanisms of RIL₂ Organo-IP₃-iodanes (Continued)

Single-Electron Transfer

Single-electron transfer from phenol ethers to IP₃-iodanes generates an arene cation radical resulting in a direct nucleophilic substitution.

The method for reactivity umpoling of diaryl-, alkenylaryl-, and alkynylaryl-IP₃-iodanes involves the generation of organochromium(III) and nucleophilic addition to aldehydes is shown below.
Reactivity of $R_2L$ Organo-$^3\beta$-iodanes

(2) $R_2L$: Acts mainly to transfer a carbon ligand (R) to nucleophiles with reductive elimination of ArL. The nature of the carbon ligands are important in determining reactivity.

**Alkyl(aryl)-$^3\beta$-iodanes**: Generally labile and decompose readily by heterolysis of C-I bond and reductive elimination of ArL.

\[ \text{BF}_3\text{-catalyzed ligand exchange of allylsilane, germane, or stannane with iodosylbenzene generates alkyl-$^3\beta$-iodane.} \]

This is a highly reactive species that is equivalent to an allyl cation. Also may serve as a perfluoroalkylating agent.

**Alkenyln(aryl)-$^3\beta$-iodanes**

Progenitor of alkyldene carbene that are formed by base abstraction of an acidic $^\beta$-hydrogen of an alkenyln-$^3\beta$-iodane. The free alkyldene carbene can form solvent-alkyldene carbene complexes (i.e. in ethereal solvents an oxonium ylide is observed).

Performs nucleophilic vinyl substitution by $S_N2$ reaction with inversion of configuration. Nucleophiles that undergo vinyl $S_N2$ reactions are sulfides, selenides, carboxylic acids, amides, thioamides, and phosphoroselenoates.

Reactivity of RIL$_2$ Organo-$^3\beta$-iodanes (Continued)

**Alkynyln(aryl)-$^3\beta$-iodanes**

The highly electron-deficient nature of the $^\beta$-acetylenic carbon atom make these reagents good Michael acceptors towards soft nucleophiles (O, N, and S) and undergo tandem Michael-carbene insertion (MCI) to give cyclopentene annulation products. (i.e. substituted furans)

Because the electron-deficient nature of the carbenic center of the alkyldene carbene, nucleophiles with high tendency to migrate undergo Michael-carbene rearrangements (MCR). When the migratory aptitude of a nucleophile is poor, the MCI pathway competes with the MCR reaction

Other useful reactions include Diels-Alder reactoins, 1,3-dipolar cycloadditions, and reactions with transition metal complexes.
Transformations Enacted by Hypervalent Iodide Reagents

- C-C Bond Bond Forming Reactions
  - Radical Decarboxylation of Organic Substrates
  - Spiroalkylation of para- and ortho-Substituted Phenols
  - Intramolecular Oxidative Coupling of Phenol Ethers
  - Reactions of Iodonium Salts and Ylides

- C-Heteroatom Bond Forming Reactions (N, O, P, S, Se, Te, X)
  - Reactions of Aryl-[3]-iodanes
  - Arylations and Alkenylations of Nucleophiles
  - Reactions of Alkynyliodinium Salt
  - Cyanation with Cyanobenzodioxoles
  - Aziridinations and Amidations by Sulfonyliminoiodane
  - Reactions of Iodonium Enolates

- Heteroatom-Heteroatom Bond Forming Reactions
  - Reactions of Aryl-[3]-iodanes
  - Reactions of Sulfonylimino(aryl)iodanes

- Oxidations and Rearrangements
  - Sulfides from Sulfides
  - Oxidations of Alcohols, Phenols, Heteroaromatic Compounds
  - Functionalization of Carbonyl Compounds
  - Functionalization in the [1]-position
  - Forming [2,3]-Unsaturations
  - Oxidation of C-H Bonds
  - Rearrangements

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**C-C Bond Forming Rxns: Radical Decarboxylative Alkylation of [Bis(acyloxy)iodo]arenes**

\[
\text{OCOR} + \text{PN(CO2)} \rightarrow \text{Hg - N} [\text{or } \text{O}] \rightarrow \text{R}^1
\]

- **Alkylation of Nitrogen Heterocycles**
  - Where R = 1-adamantyl, cyclohexyl, 2-PhCH2, PhOCH2, Ph(O), etc. and
  - ![Chemical Structures]

- **Radical Alkylation of Electron-Deficient Alkenes**
  - Yield of products depends on the stability and nucleophilicity of the alkyl radicals (tertiary > secondary > primary).
  - Where Z = SO2Ph, SOPh, CO2Me, P(O)(O)Et2; R' = H, Me
  - R = 1-adamantyl, cyclohexyl, 2-PhCH2CH2, etc.
**C-C Bond Forming Rxns: Oxidative Cyclization of Phenols and Phenol Ethers**

![Chemical diagram showing the reaction of phenol ethers with Pd(OAc)₂, leading to the formation of a phenol ring with an internal nucleophile.]

Important in constructing various polycyclic systems from p- or o-substituted phenols with an external or internal nucleophile like alcohols, fluoride ions, amines, aldehydes, and electron-rich aromatic rings.

Example:

Oxidation of phenol ether in the presence of an external or internal nucleophile affords products of nucleophilic substitution via formation of a cation radical intermediate.

**Examples in Total Synthesis: Epoxyisorbiclillinol and Bisorbiclillinol**

- Hypervalent Iodide(III) Induced Oxidative Dearomatization

![Chemical diagram showing the preparation of Epoxyisorbiclillinol and Bisorbiclillinol from a precursor through the use of palladium and iodine reagents.]

(Pettus, Org. Lett. 2001, 3, 905)
Examples in Total Synthesis: Quinone-Imine Formation in Dynemicin A

- Danishefsky's Approach (J. Am. Chem. Soc. 1996, 118, 9509)


C-C Bond Forming Rxns: Reactions of Iodonium Salts

- Stabilized Alkylodonium Salts

Diagrams and structures are shown illustrating the chemical reactions and structures involved in the total synthesis of Dynemicin A.
**C-C Bond Forming Rxns: Reactions of Iodonium Salts (Continued)**

### Stabilized Alkenylidonium Salts

**Generation of Alkylidene carbenes**

![Chemical structure](image)

**Alkenylation of C-Nucleophiles**

![Chemical structure](image)

Transition Metal Mediated Cross-Coupling with Cu, Zn, Sn, Pd

### Stabilized Arylidonium Salts

**Arylation of C-Nucleophiles**

![Chemical structure](image)

**Generation of Benzenes**

![Chemical structure](image)

### Alkynylidonium Salts

**Example of Indole Synthesis**

![Chemical structure](image)

**Example of [4+2] Cycloaddition**

![Chemical structure](image)
**C-C Bond Forming Rxns: Reactions with Iodonium Ylides and Cyanation**

- **Reactions with Iodonium Ylides**

  ![Diagram of C-C Bond Forming Reaction](attachment:reaction_diagram.png)

  Intramolecular Cycloaddition Example:

  ![Intramolecular Cycloaddition Example](attachment:intramolecular_example.png)

- **Cyanation with Cyanobenziodoxoles**

  ![Cyanation with Cyanobenziodoxoles](attachment:cyonation_diagram.png)

  Prepared in one step by cyanomethylsilane and hydroxybenziodoxoles and a stable radical precursor for an otherwise unstable i-CN bond. Efficient cyanating agents towards N,N-dialkylamines.

**C-Heteroatom Bond Forming Rxns: Aryl-[^\]^-iodanes**

- **Azidation**

  Applications have been on TIPS enol ethers, glycalis, dihydropyranos, aryl N,N-dialkylamines, cyclic amides, and cyclic sulfides.

  ![Diagram of Azidation Reaction](attachment:azidation_diagram.png)

- **Oxidative Addition of C,C-Multiple Bonds**

  **C,C-Double Bonds** DBB with appropriate reagents results in co-introduction of equivalent/ non-equivalent heteroatom groups.

  Dithiocyanation: TMSNCS
  Phenylselenyl-thiocyanation: TMSNCS and (PhSe)$_2$
  Phenylselenyl-acetoxylation: (PhSe)$_2$
  Azido-phenylselenation: NaN$_3$ and (PhSe)$_2$
  Haloacetoxylation: Ph$_2$PT
  Haloazidation: Et$_3$N^+X^- and TMSN$_3$

  **C,C-Triple Bonds**

  ![Diagram of C,C-Triple Bond Oxidative Addition](attachment:triple_bond_diagram.png)
C-Heteroatom Bond Forming Rxns: Aryl-[β]-iodanes (Continued)

- Functionalization of Aromatic Compounds

- Functionalization of Carbonyl Compounds

- C-Fluorine Bond Formations

  $p$-(Difluorocido)toluene (DFT) with appropriate reagents results in C-fluorine bond formation.

  vicinal difluorination of terminal alkenes: $\text{Et}_2\text{N}^-\text{SHF}$

  trans-difluorination of terminal alkenes: $\text{Et}_2\text{N}^-\text{SHF}$ then CuI/KI

  monofluorination of β-dicarbonyl: (DFT generated in situ)

  difluorination of difluoroketal of benzophenone (to diarylfluoromethanes): (in situ generated $p$-(difluorocido)anisole)

  fluorination of β-phenyl ketones and lactones: (DFT-induced fluoro-Pummerer reaction)

  alcohols to $1^-$ and $2^-$alkyl fluorides: conversion to xanthate esters followed by DFT

C-Heteroatom Bond Forming Rxns: Diaryliodonium and Alkenyliodo(aryl)iodonium Salts

- Diaryliodonium Salts

- Alkenyliodo(aryl)iodonium Salts

  Alkenylation of heteroatom nucleophiles occurs by a variety of mechanisms; $\text{S}_2\text{Ar}$, $\text{S}_2\text{Z}$, alkylidene carbene, and addition-elimination pathways.
C-Heteroatom Bond Forming Rxsns: Alkyny(aryl)iodonium Salts

- **Alkynylation**
  
  ![Alkynylation Reaction](image)

- **C-H Bond Insertions**
  
  ![C-H Bond Insertion](image)

Intramolecular C-H bond insertions result in bicyclizations

C-Heteroatom Bond Forming Rxsns: Alkyny(aryl)iodonium Salts and Enolates

- **C-Heteroatom Bond Insertions**
  
  ![C-Heteroatom Bond Insertion](image)

- **Cyclocondensations**
  
  ![Cyclocondensation](image)

- **Iodonium Enolates**
  
  ![Iodonium Enolate](image)

Example: 

\[
\text{AcO}^- + \text{H}^+ \rightarrow \text{HCOO}^-
\]

\[
\begin{align*}
\text{AcO}^- + \text{H}^+ &\rightarrow \text{HCOO}^- \\
\text{X} &\rightarrow \text{BF}_3; R &\rightarrow \text{Me}, \text{C}_6\text{H}_{13}, \text{Bu}
\end{align*}
\]

\[
R = \text{RC}_2\text{H}_4 (R = \text{H}, 2-\text{Me}, 4-\text{Me}, 4-\text{F}, 4-\text{Cl}, 4-\text{Br}, 4-\text{NO}_2), \text{Et}, \text{n-C}_6\text{H}_{13}, \text{Ph}, \text{Bu}, (E)-\text{MeCH} = \text{CH}
\]
C-Heteroatom Bond Forming Rxns: Sulfonylimino(aryl)iodanes

**Azidation**
Phl=NTs as a nitrile transfer agents has been demonstrated with Mn(III)- and Fe(III) porphyrins and more generally with Cu(I)/Cu(II) salts (Evan's azidation reaction) on cyclic acyclic alkenes, alkylalkenes, and B-unsaturated esters.

![Diagram of azidation reaction]

Product yields increase with substitution on the arenesulfonfony moiety (p-OMe > p-Me > p-NO2).
Chiral ligands (isoaxazolines) and bis(benzylidene)diamino cyclohexanes give asymmetric tosylationazidations (e.g. = 66%-94%).
More reactive are [nitosylimino]iodo]benzene (Phl=NN) and (2-trimethylsilyl)ethanesulfonfony]iodo)benzene (Phl=NSes).

**Amidations**
Chiral allylic and benzylcyclopropanamidations are performed with salen-Mn(III) complexes, Ru(II) and Mn(III)-porphyrins, and Ru(II) and Ru(III)-amine complexes as catalysts. (e.g. = 41-67% for cyclic compounds and 12-93% for acyclic compounds)

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**Heteroatom-Heteroatom Bond Forming Rxns**

**Ar-O-aryl-iodanes: Oxidation of S, P, Se, Te, Sn, & Bi**

**Sulfide Oxidation**

![Diagram of sulfide oxidation]

**Diaryldisulfide Oxidation**

![Diagram of diaryldisulfide oxidation]

**Sulfonylimino(aryl)iodanes: Constructing P-N, S-N, Se-N, As-N Bonds**

**Phosphorous and Arsenic Ylide Formation**

![Diagram of phosphorous and arsenic ylide formation]

**Phl=NTs Reaction Products**

![Diagram of Phl=NTs reaction products]
Summary of Oxidations with Hypervalent Iodine Compounds

- Chalcogen Oxidation
  Sulfides to sulfoxides with IBX and BTI.
  Disulfides to sulfonic esters or thiosulfonic S-esters.
  Dithiolenes to selene sulfonates.
  Dithiurilnes to mixed arenethiuluric anhydrides.

- Alcohols to Carboxyls
  **Iodine (V) Reagents**
  DMP or IBX: alcohol to aldehydes & ketones
  IBX + Wittig Ylides: benzylic, allylic, propargylic
  alcohol to [I)n unsaturated ester
  (water soluble reagent) benzylic, allylic, propargylic alc. oxidation

  **Iodine (III) Reagents**
  DIB + TEMPO: selective 1° alcohol to aldehyde
  IOD + cat. KBr: 1° alcohol to ROOH,
  2° alcohol to ketone
  DIB + TMSNO₂⁻: desilation and oxidation of glycols

- Oxidations of Phenols
  **Iodine (V) Reagents**
  IBX: Phenol to ortho-quinone only
  DMP + water: Anilides to α-imidoquinones and
  p-anilines to para-quinones

  **Iodine (III) Reagents**
  BIT or DIB: Phenols to quinones by oxidations at
  α- or p-position.
  DIB + water: Phenols or anilines to p-quinones

- Oxidations of Heteroaromatic Compounds
  Aromatization of 5 and 6 membered rings using BIT or DIB

Oxidations & Rearrangements Using Hypervalent Iodine Compounds

- [Functionalization of Carbonyl Cmpds]
  (Nucleophilic attack on phenylkated intermediate)
  IBX/BID/IOB + base: Yields 1°hydroxylated acetals
  HTI: Tosylation of ketone (silyl enol ethers)
  Tosylation with about 40% e.e.

- [Introduction of Unsaturation]
  Dehydogenation of enone via in situ
  formation of silyl enol ether
  IBX: Dehydogenation by single electron transfer process

- [Oxidation of C-H Bonds]
  1°-8°: Oxidation of benzylic, allylic, or propargylic
  ethers to esters by a radical process.
  2°: Removal of benzyl ether protecting group

Rearrangements

- Hofmann-type Rearrangements
  BID: Cyclizations of aromatic amidines with a nucleophile in the
  ortho-position.

  [Diagram showing rearrangement process]

Rearrangement of Amidines

- BID: Forms urea derivatives via carbodiimide intermediate.

  [Diagram showing rearrangement process]

Cyclization of Unsaturated Carboxylic Acids

- [Diagram showing cyclization process]
Rearrangements Using Hypervalent Iodine Compounds

Rearrangements (Continued)

Rearrangement of Cumarines
DIB: 1,2-phenyl migration and formation of [\(\alpha\)acetal]

Iodonio-Claisen Rearrangement
Alkanyl(phenyl)iodine(III) compounds or DIB derivatives + propargyl silanes: Access to propynyl cmpds.

Alkynyl(phenyl)iodine(III) compounds:
Thioamides yield thiazoles
Furan derivative ring enlargements to yield pyrones

Conclusions and Future Direction of the Hypervalent Iodine Chemistry

Future Goals

Searching for newer reagents that will lead to new reaction transformations.
Recyclable polymer supported reagents
Broadening the scope of reactivity by studying transition metal-mediated reactions

Conclusions

The chemistry of hypervalent iodine reagents is cool because:

1. Fundamental reactions with versatility have been developed
2. Mild reactivity with good yields
3. Readily available reagents that are easy to work with
4. Non-toxic, environmentally-friendly reagents